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Depression and the Usefulness of a Disease Management Program in Heart Failure

Insights From the COACH (Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure) Study

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Objectives Our aim was to study the possible role of depressive symptoms in the effectiveness of a disease management program (DMP) in heart failure (HF) patients.

Background Disease management programs are recommended in current HF guidelines, but certain patient groups, such as those with depression, might be less responsive to such programs.

Methods From the data of a large multicenter study, in which we examined the effect of a DMP in HF patients, we investigated a potential interaction between depressive symptoms at baseline and the effect of such a program.

Results Of the 958 HF patients (37% female; age 71 ± 11 years; New York Heart Association functional class II to IV), 377 (39%) reported depressive symptoms at baseline. During 18 months of follow-up, the primary end point (composite of all-cause mortality and HF readmission) occurred in 39% of the nondepressed patients and 42% of depressed patients. In the overall sample, there was no significant effect of DMP on the composite primary end point. The effect of the DMP was significantly different in nondepressed than in depressed HF patients. A significant effect modification by depressive symptoms was observed in evaluating the effect of the DMP on all-cause mortality and HF readmission ($p = 0.03$). In patients without depressive symptoms, DMP resulted in a trend for lower incidence of the primary end point (hazard ratio: 0.8, 95% confidence interval: 0.61 to 1.04), whereas the reverse was observed in patients with depressive symptoms (hazard ratio: 1.3, 95% confidence interval: 0.95 to 1.98).

Conclusions Depressive symptoms in patients with HF have a major effect on the usefulness of DMP. Identification of depressive symptoms before enrollment in a DMP might lead to more accurate use of a DMP, because depressive patients might not benefit from a general program. (Netherlands Heart Foundation Coordinating study evaluating Outcomes of Advising and Counselling in Heart Failure; ISRCTN98675639) (J Am Coll Cardiol 2010;55: 1837–43) © 2010 by the American College of Cardiology Foundation

Implementation of disease management programs (DMPs) for heart failure (HF) patients are a class I recommendation in the current HF guidelines (1,2). Despite several studies reporting on decreased readmission and mortality rates, it is not yet clear what the most optimal model of HF management is. There are key features of successful DMPs; however, there still is a need for improvement of existing programs and for defining an optimal approach for specific patient groups (3–5).

Depression is a major problem in HF patients, and the prevalence of depressive symptoms in HF patients is significantly higher compared with an age- and sex-matched population (6,7). Patients with depressive symptoms have worse outcomes in terms of readmission rate and mortality and are described as having considerably increased health care costs (8,9). One would reason that the best remedy to improve outcomes might be to cure the depression. However, recent studies report only limited effects of psychotherapy and antidepressant medication treatment on outcomes of depression in cardiac patients, and no intervention studies in depressive HF patients are currently known (10,11).

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Abbreviations and Acronyms

CES-D = Center for Epidemiological Studies Depression Scale
CI = confidence interval
DMP = disease management program
HF = heart failure
HR = hazard ratio
LVEF = left ventricular ejection fraction
NYHA = New York Heart Association

Depressive symptoms are a risk factor for nonadherence with the HF regimen, such as medication, diet, and exercise. Nonadherence in turn is known to be related to increased readmission and mortality (12–15). Improving adherence by increasing knowledge and skills of patients is the goal of DMPs. These programs assume an active role for motivated patients and therefore might be less suitable for depressive patients. To study this possible role of depression in HF management, we analyzed patients with and without depressive symptoms enrolled in the COACH (Coordinating study evaluating Outcomes of Advising and Counseling in Heart failure) study (16).

Methods

Design and intervention. The methods and primary results of the COACH study have been previously reported (16,17). The COACH study is a randomized controlled trial investigating the effect of a DMP on readmission for HF and mortality. Patients were randomly assigned into 1 of the treatment strategies: 1) basic support; 2) intensive support; or 3) a control group. Patients assigned to the control group received routine management by the cardiologist and general practitioner. No additional follow-up by an HF nurse was provided. Basic support consisted of patient education, additional visits to an HF nurse every 3 months, and telephone access to an HF nurse during office hours. Intensive support additionally included monthly contact with an HF nurse, multidisciplinary advice, home visits, and 24-h access to an HF team during 18 months.

Patients. Patients were included in the study during admission for HF (New York Heart Association [NYHA] functional class II to IV), with HF as the primary diagnosis (16). All patients had been admitted to the hospital with HF symptoms and were classified as NYHA functional class II to IV. The diagnosis was made on the basis of a combination of typical signs and symptoms for which hospital stay was considered necessary, including the need for intravenously administered medication. Patients were 18 years or older and had evidence of structural underlying heart disease as shown at cardiovascular imaging. Both patients with impaired left ventricular ejection fraction (LVEF) and those with preserved LVEF could participate. Reasons for exclusion were: concurrent inclusion in a study requiring additional visits to research health care personnel; restrictions that make the patient unable to fill in data collection forms; invasive intervention within the last 6 months (percutaneous transluminal coronary angioplasty, coronary artery bypass graft, heart transplantation, valve replacement) or planned during the following 3 months; or ongoing evaluation for heart transplantation. The study complied with the Declaration of Helsinki, and a central appointed ethics committee approved the research protocol. Informed consent was obtained from the subjects.

Data collection. DEPRESSIVE SYMPTOMS. Data on depressive symptoms were collected with the Center for Epidemiological Studies Depression Scale (CES-D). This is a valid instrument that has been established in cardiac and noncardiac patients (18) to identify high-risk patients and study the relationships between depressive symptoms and other variables. A total sum score is calculated (0 to 60), with higher scores indicating more depressive symptoms. A cutoff point of 16, which is generally used to define patients at risk for clinical depression, was used to distinguish between HF patients with depressive symptoms (CES-D $\geq$16) and patients without depressive symptoms (CES-D $<$16).

Data were collected during hospital stay shortly before discharge from the hospital when patients were clinically stable.

END POINTS. Primary end points were time-to-death or readmission for HF and the number of days lost to death or readmission (unfavorable days). Major secondary end points were mortality and readmission. Data regarding readmission and mortality were collected and adjudicated by an independent end point committee.

DEMOGRAPHIC AND CLINICAL DATA. Data were collected from patient chart and interview.

Statistical analysis. Baseline characteristics of patients with depressive symptoms (CES-D $\geq$16) and without depressive symptoms (CES-D $<$16) in the control and intervention groups were summarized by mean (SD) for continuous variables and by frequency for categorical variables. Kaplan-Meier curves were constructed for the different time-to-event evaluations. To estimate effect sizes, hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated with multivariable Cox proportional hazards regression models. In these analyses, effect modification of intervention by the presence of depressive symptoms was specifically considered by including interaction terms in the models. Because no differences were found between patients in either intervention group (basic and intensive), data were pooled for the 2 intervention groups and compared with the control group. Because the proportion of women and patient NYHA functional classification in the control and intervention groups was significantly different between the patients with and without depressive symptoms, we adjusted for NYHA functional classification and sex in all Cox regression analyses. A p value of $<$0.05 was taken as the level of significance. Differences regarding the unfavorable days and number of readmissions were analyzed with chi-square and Mann-Whitney tests.

The funding source (the Netherlands Heart Foundation) did not have any role in collecting, analyzing, or interpreting the data or in writing or submitting the report.

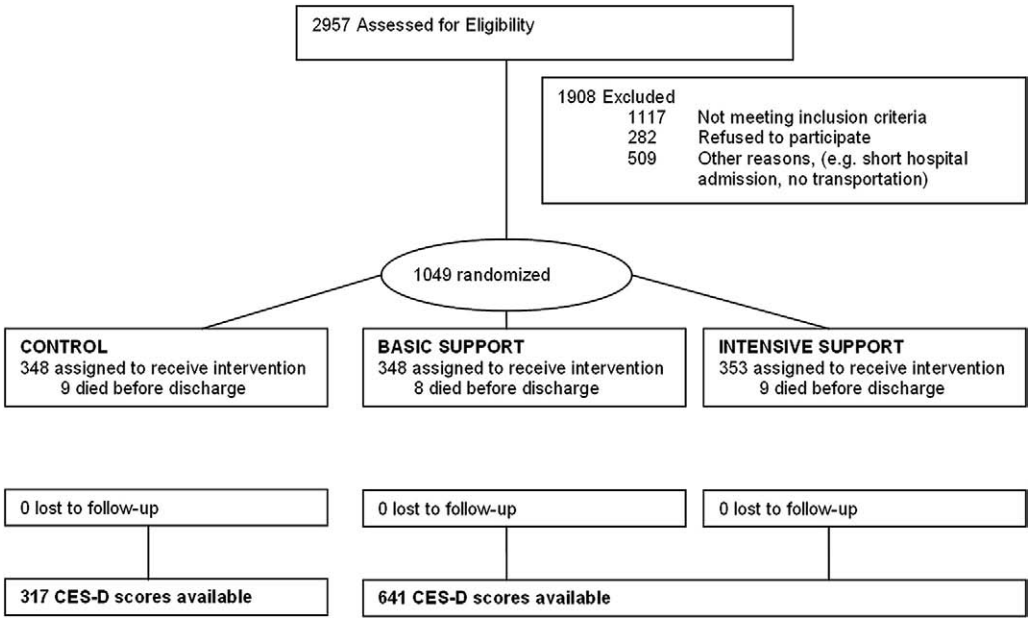

Figure 1 **Flow of Participants**

Enrollment and follow-up of the patients in the trial (consort diagram). Patient data in the 2 intervention groups (basic support and intensive support) were pooled into 1 group. CES-D = Center for Epidemiological Studies Depression Scale.

Results

Study sample. Of the 1,023 included patients, data on depressive symptoms at baseline were available in 958 patients (Fig. 1). The mean age of the patients was 71 ± 11 years, and 63% were men (Table 1). At admission most patients were classified as NYHA functional class III or IV, and at discharge 51% were NYHA class II and 49% were NYHA class III or IV. Both patients with systolic HF and with a preserved LVEF were included; the mean LVEF was 34 ± 15%, and 43% of the patients had HF with ischemic etiology. At discharge, 96% of the patients were prescribed a diuretic, 83% were prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and 66% were prescribed a beta-blocker.

Of the total sample of 958 patients, 377 patients (39%) reported depressive symptoms at baseline (CES-D ≥16). Of the depressed patients, 11% used antidepressive medication. Depressed patients were more often female and had a higher NYHA functional classification at discharge. No differences were found between depressed and nondepressed patients in other variables, such as age, LVEF, or HF medication.

Interaction between outcome and depressive symptoms.

PRIMARY END POINT: HF HOSPITALIZATION OR DEATH. We found a statistically significant effect modification by depressive symptoms in the effect of the DMP on the primary end point—HF readmission and all-cause mortality—that is, there was a difference in the effect of the intervention in depressed and nondepressed patients; uncorrected, p = 0.05; corrected for NYHA functional class and sex, p = 0.03. Hazard ratios are presented for the depressed and nondepressed patients separately.

Nondepressed patients. A total of 39% of the 581 nondepressed patients were hospitalized for HF or died within the 18 months of the study. Patients in the DMP reached their primary end point less often (36%) than patients in the control group (44%), although this effect did not reach statistical significance (HR: 0.8; 95% CI: 0.60 to 1.03, p = 0.08). After correction for NYHA functional classification and sex, the HR remained 0.8 (95% CI: 0.61 to 1.04, p = 0.11) (Fig. 2).

Depressed patients. Of the 377 depressed patients, a total of 41% were hospitalized for HF or died within the 18 months of the study. In contrast to the nondepressed patients, depressed patients did not benefit from the DMP. Patients in the DMP more often reached the primary end point (46%) compared with patients in the control group (37%) with an HR of 1.5 (95% CI: 1.04 to 2.15, p = 0.03). After adjusting for NYHA functional classification and sex, this effect lost statistical significance with an HR of 1.3 (95% CI: 0.95 to 1.98, p = 0.12).

PRIMARY END POINT: UNFAVORABLE DAYS. Patients without depressive symptoms had fewer unfavorable days compared with patients with depressive symptoms (median of 8 days vs. 11 days, p = 0.059). Nondepressed patients in the DMP group had significantly fewer unfavorable days than nondepressed patients in the control group (median of 7

Table 1 Baseline Characteristics According to Group Assignment and Depressive Symptoms

	All (n = 958)	No Depressive Symptoms (n = 581)		Depressive Symptoms (n = 377)	
		Control (n = 201)	Intervention (n = 380)	Control (n = 116)	Intervention (n = 261)
Demographic variables					
Age, yrs	71 ± 11	73 ± 11	70 ± 12	69 ± 12	70 ± 12
Female sex	37%	34%	32%	51%	40%*
Clinical variables					
LVEF, %	34 ± 15	33 ± 14	33 ± 14	36 ± 15	34 ± 16
History of AF	36%	36%	35%	35%	39%
NYHA (at discharge)					
II	51%	57%	55%	51%	41%*
III–IV	49%	43%	45%	49%	59%
Ischemic etiology	43%	47%	44%	32%	44%
≥1 comorbidity	79%	78%	76%	84%	81%
Prior HF admission	67%	65%	71%	66%	66%
Medication at discharge					
ACE/ARB	83%	82%	83%	83%	83%
Diuretics	96%	95%	96%	97%	95%
Beta-blockers	66%	68%	65%	66%	67%
Lipid-lowering drugs	38%	41%	39%	34%	36%
Antidepressants	7%	7%	3%	10%	12%
Depression					
CES-D total score	15 ± 11	8 ± 4	8 ± 4	27 ± 9	26 ± 8

Values are mean ± SD or %. *p < 0.05.
ACE/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; AF = atrial fibrillation; CES-D = Center for Epidemiological Studies Depression Scale; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA= New York Heart Association functional class.

days vs. 15 days, p = 0.029). The reverse was found in patients with depressive symptoms where patients in the control group had fewer unfavorable days than patients in the DMP group (median 2 vs. 18 days, p = 0.001).

SEPARATE COMPONENTS OF THE PRIMARY END POINT: MORTALITY AND HF READMISSION: MORTALITY. A total of 26% of the nondepressed and 29% of the depressed patients died within the study period of 18 months. A significant effect

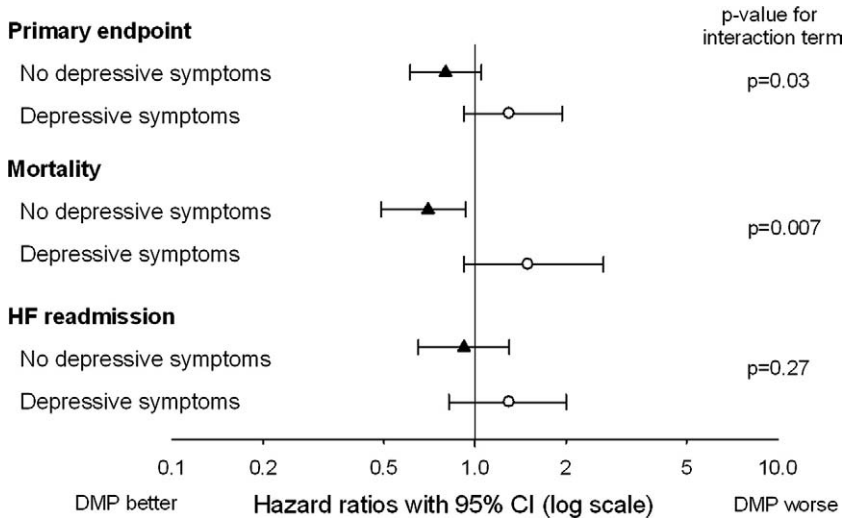

Figure 2 Interactions Between Depression and Intervention and Hazard Ratios for Depressed and Nondepressed Patients

Interactions (p values) between the presence of depression and the effect of the intervention (disease management program [DMP]), hazard ratios and the 95% confidence intervals (CIs) for the patients with depressive symptoms (n = 377) and no depressive symptoms (n = 581) separately, corrected for New York Heart Association functional class and sex. HF = heart failure.

modification of group assignment by depressive symptoms was found for mortality (uncorrected p = 0.002, corrected for NYHA functional class, p = 0.007).

Nondepressed patients in the DMP had significantly lower mortality (22%) compared with patients in the control group (32%) (HR: 0.7, 95% CI: 0.49 to 0.93, p = 0.02) and after correction for NYHA functional class and sex (HR: 0.7, 95% CI: 0.49 to 0.94, p = 0.02) (Fig. 2).

Depressed patients in the DMP had a higher mortality rate (32%) versus depressed patients in the control group (21%) (HR: 1.6, 95% CI: 1.09 to 2.46, p = 0.04). After correction for NYHA functional class and sex, this effect lost statistical significance (HR: 1.5, 95% CI: 0.94 to 2.39, p = 0.11).

SEPARATE COMPONENTS OF THE PRIMARY ENDPOINT: HF READMISSION. A total of 26% of the nondepressed and 28% of the depressed patients had an HF readmission. There was no significant effect modification of group assignment by depressive symptoms HF readmission (p = 0.27) (Fig. 2).

ALL-CAUSE READMISSION. Overall, in patients without depressive symptoms the DMP led to lower readmission rates; in patients with depressive symptoms the reverse was found (Table 2). The relationship of all-cause readmission and the DMP was modified significantly by depressive symptoms (p value for interaction = 0.02). Also after correction for NYHA functional class and sex, depressive patients in the DMP had significantly higher readmission rates compared with depressed patients in the control group (HR: 1.47, 95% CI: 1.08 to 1.99, p = 0.01). In the nondepressed patients, patients in the DMP had slightly fewer readmissions than patients in the control group (Table 2); however, this was not statistically significant (HR: 0.89, 95% CI: 0.70 to 1.12, p = 0.32).

Discussion

The main finding of the present study is that depressive symptoms have an impact on effectiveness of DMP in HF patients. Specifically, in patients without depressive symptoms the DMP significantly decreased the number of days lost to death or readmission and reduced mortality rates. In contrast to these findings, we found that in patients with depressive symptoms the DMP did not lead to an expected reduction in readmissions but led to an increase in readmissions. Additionally, depressed patients did not have a mortality benefit from the DMP.

These data shed new light on the importance of tailoring interventions to individual patients and can be used to improve DMPs. Patients with depressive symptoms should probably not be included in a general HF management program that is not specifically targeted at managing depressive symptoms and their consequences.

The primary objective of the COACH study was to test whether a DMP consisting of education and support by a nurse could lead to reduced HF readmission and mortality. Inclusion criteria were liberal, and patients are representative of patients in daily practice. Patients with overt psychiatric disorders were excluded, but a high percentage of patients (39%) were found to have depressive symptoms, identified by a validated questionnaire. The intervention in the COACH study mainly focused on adherence to lifestyle changes, symptom recognition by patients, and consultation with a health care professional for changes in symptoms. Although psychosocial issues of patients were addressed in the training of the nurses, and worries and feelings of patients were assessed and discussed, no specifically tailored intervention was available for patients with depressive symptoms. This is in line with most DMPs that offer similar interventions to depressed and nondepressed patients and that do not specifically address comorbid (mental) illnesses (19).

Depression—with its associated lack of motivation, helplessness, and lack of energy—is known to obstruct active participation in lifestyle changes and symptom recognition needed for taking appropriate action in case of worsening symptoms (20). The goals of the intervention were apparently realistic and obtainable for nondepressed patients but not for depressed patients in whom it might have had a deleterious effect when compared with a less intrusive treatment regimen (standard care). One can imagine that depressed patients are less amendable or responsive to an intervention. They might have felt confronted with the disease and with their limitations by the attention drawn to it by the health care professionals in the DMP. Patients might well have somaticized more, and the increased awareness of symptoms by both patients and health care providers in the DMP combined with the difficulty of correctly interpreting and treating symptoms of depressed

Table 2 Readmission Rates According to Group Assignment and Depressive Symptoms

		No Depressive Symptoms (n = 581)			Depressive Symptoms (n = 377)		
	All (n = 958)	All (n = 581)	Control (n = 201)	Intervention (n = 380)	All (n = 377)	Control (n = 116)	Intervention (n = 261)
All-cause readmission	56%	53%	56%	52%	60%	50%*†	64%*†
CV (including HF) readmission	43%	41%	45%	39%	45%	38%*‡	48%*‡
HF readmission	26%	24%	25%	23%	28%	24%	30%
Non-CV readmission	27%	24%	25%	24%	30%	26%	32%

*Control versus intervention in patients with depressive symptoms; †p < 0.01; ‡p < 0.05.
CV = cardiovascular; HF = heart failure.

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HF patients could have resulted in an increased readmission rate. Depressive patients probably feel more demoralized, given their health status, and for them it is probably more difficult to take advantage of the intervention compared with nondepressed patients, who also have decreased health status but might be more capable and motivated to take advantage of the advice of the nurse.

Although these are mere hypothetical explanations, similar findings have been reported in a study in myocardial infarction (MI) patients by Frasure-Smith et al. (21), who found that a nurse-led intervention in MI patients had a harmful impact on depressed women. They also report that increased contact with a nurse might have reminded patients of their MI and increased distress.

These results raise the issue of how to optimally manage these complex patients that suffer from both physical and psychological symptoms. That psychosocial problems are underestimated and undertreated in HF patients (22,23) was confirmed by the present finding that only 10% to 12% of the patients with depressive symptoms were prescribed antidepressant medication. Although we did not assess a clinical diagnosis of depression but rather the presence of depressive symptoms, the CES-D is a well-validated scale that does identity patients who are at high risk of developing a depressive disorder. Earlier studies have shown that, even in HF patients with a clinical diagnosis of depression, only 27% to 33% received antidepressant medication (24). Depressive symptoms need to be recognized during enrollment in a DMP. For these patients a standard DMP should not be applied, and a tailored intervention addressing both psychological and HF aspects is probably more suitable. This implies that a multidisciplinary approach is needed to combine issues specifically related to HF and more psychological problems, focusing on HF-specific lifestyle changes and optimization of HF medication, antidepressants, and counseling (25).

Nondepressed patients in this study seemed to benefit from the intervention by lower primary end point. The intervention in the study assumed an active role for patients by education on symptom recognition and lifestyle changes, which is known to decrease mortality and readmission (26,27).

Study limitations. This present study has a few potential limitations. Because the analyses are subgroup analysis and this study was not designed to prospectively follow depressed and nondepressed patients, the results should be interpreted with caution. Secondly, although used in previous publications (17,28), the rather novel end point of "unfavorable days" might be challenging to interpret. Nevertheless, we believe the presented data can generate new hypotheses and shed new light on the implementation of DMPs in HF patients.

Conclusions

This study showed that depressive symptoms in patients with HF have a major effect on the usefulness of DMPs. Nondepressed HF patients can benefit from a DMP mainly focusing on education and counseling, whereas patients with depressive symptoms do not benefit in terms of mortality or readmission. A more specific approach for depressed patients is needed in which a conjoint therapy of HF management and psychological problems could be successful and in which special attention is given to adherence and psychopharmacology.

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Key Words: depressive symptoms ■ disease management ■ heart failure.